REMARKS

Applicants appreciate the entry of the Amendment filed 17 March 2005, and the Examiner's consideration of the Information Disclosure Statement submitted on 17 March 2005. Applicants have amended claims 35 and 43. No new matter has been added by way of amendment. Claims 35, 38-40, 43, and 46-48 will be pending upon entry of the instant amendment.

The Rejection of Claims 35, 38-40, 43, and 46-48 under 35 USC §112 (Enablement), Should Be Withdrawn

The Examiner rejected claims 35, 38-40, 43, and 46-48 under 35 USC §112, first paragraph, as failing to comply with the enablement requirement. The Examiner stated that the claim(s) contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Specifically, the Examiner argued, "the instant specification fails to teach how to achieve the proposed binding assay, thus requiring undue experimentation of one skilled in the art to use the claimed invention with a reasonable expectation of success." The Examiner also stated that "the art teaches that the ability to deliver proteins into cells, where one of skill in the art would expect the COE-2 protein (SEQ ID NO:2) to be localized, is problematic due to the bioavailability restriction imposed by the cell membrane. The plasma membrane of cells forms an effective barrier which restricts the intracellular uptake of molecules to those which are sufficiently non-polar and smaller than approximately 500 daltons in size (see Wadia et al. (2003)," and, "Therefore, one skilled in the art would not know, with any level of predictability, that a method comprising combining a compound with a sample comprising a cell expressing the COE-2 polypeptide (SEQ ID NO:2) would result in the binding of the compound to the COE-2 polypeptide."

The Examiner also argued that "the specification also fails to disclose sufficient information on how to assess the binding of the candidate compound to the COE-2 polypeptide (SEQ ID NO:2). In the absence of this guidance, a practitioner would have to resort to a substantial amount of undue experimentation to practice the invention..."

The Examiner further stated,

> "There are no working examples presented in the instant specification that describe compounds which bind to the COE-2 polypeptide (SEQ ID NO:2). The specification fails to disclose whether or not candidate compounds can be targeted to the COE-2 polypeptide, which based on the teachings of the prior art and the instant specification, is located intracellularly. Therefore, the person of ordinary skill in the art would not be able

to use the method to identify a candidate compound capable of binding to a COE-2 polypeptide because there is no reasonable expectation that compounds could be targeted to the intracellular protein and the specification as filed has not provided any guidance on how to assess the binding of the candidate compound to the COE-2 polypeptide."

Applicants traverse the rejection and submit that the screening methods of the claims are indeed described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Wadia et al., cited by the Examiner, describes the delivery of proteins into cells using protein transduction domains derived from nucleic acid binding proteins, such as HIV TAT protein. Applicants respectfully point out that Wadia et al. teaches that delivery of molecules not in excess of 500 Daltons would not likely be problematic. Thus, Applicants submit that the claimed methods with respect to screening small molecules are enabled, as one of skill in the art would have a reasonable expectation of success in using the invention. Furthermore, Applicants respectfully point out that Wadia et al. also described work done previously by McNeil et al. (April 1984, Journal of Cell Biology, 98:1556-1564, "A method for incorporating macromolecules into adherent cells) using "a process known as 'scrape-loading' which allowed the protein to enter the cell following transient mechanical disruption [14,26]." (please see page 98 of Wadia et al., second column, middle of second paragraph). McNeil et al. (submitted herewith as Supplemental Information Disclosure Statement Citation No. B7) teaches this technique, "a simple method for loading exogenous macromolecules into the cytoplasm of mammalian cells adherent to tissue culture dishes." (please see McNeil et al., abstract, first sentence). McNeil et al. describes the successful loading of a number of exogenous macromolecules into mammalian cells, including dextran in a range of molecular weights (e.g. ~10,500 mol wt; ~39,000 mol wt; and ~65,000 mol wt), ovalbumin (~ 45,000 mol wt), immunoglobulin G (~59,500 mol wt), and actin (~43,000 mol wt), with the largest molecules so delivered being dextran at 2,000,000 mol wt. (see McNeil et al., especially Figures 1 and 2, pages 1560 and 1562). Furthermore, McNeil et al. suggests that "antibodies to a variety of antigens can be loaded," (McNeil et al., page 1563, first column, last paragraph entitled, "Possible Applications of the Scrape-loading Technique"). Applicants point out that the method of McNeil et al. is referenced in the well-known laboratory techniques manual, Current Protocols in Cell Biology, in Unit 20.1 entitled "Direct Introduction of Molecules into Cells" (contributed by Paul McNeil; edited by Juan S. Bonifacino et al.; John Wiley and Sons, Inc; online posting date May 2001, print publication date October 1998, submitted herewith as Supplemental Information Disclosure Statement Citation No. B9), demonstrating that it is established, accepted and operable. Furthermore, Unit 20.1 of Current Protocols in Cell Biology also references a number of other useful methods for direct introduction of molecules into cells, including scrape loading, scratch loading, bead loading, and syringe loading. Thus, one of ordinary skill in the art would have a reasonable expectation that the candidate compounds of the instant invention, for example

small molecules, peptides, or antibodies, could indeed be targeted to the intracellular protein of SEQ ID NO:2.

Applicants point out that the specification as filed describes assays for screening candidate or test compounds which bind to COE-2 proteins (see for example, at page 47, lines 23-29 of the instant specification as filed), including how to obtain test compounds using known combinatorial library methods (see for example, at page 47, line 30 through page 48, line 1 of the instant specification as filed). The specification, for example at page 46, lines 3-16; at page 47, lines 22-30; and at page 48, line 17 through page 49, line 14, also teaches that determining the ability of the test compound to bind the COE-2 protein can be accomplished via radioisotope or enzymatic labels, by direct binding, competition binding, or immunoassay.

Applicants also submit that methods suitable for assessing the binding of a candidate compound to the COE-2 polypeptide were well known in the art at the time of filing. For example, Deutsch et al. (January 1, 2000, Cytometry, 39:36-44, Analysis of enzyme kinetics in individual living cells utilizing fluorescence intensity and polarization measurements, submitted herewith as Supplemental Information Disclosure Statement Citation No. B8) teaches an improvement on a known method of measuring kinetic events in intact living cells by assaying enzymatic activity using two "widely used" esterase substrates (please see Deutsch et al. for example in abstract; at page 37, first column, fourth full paragraph; and at page 41, first and second columns, paragraph spanning). Thus, methods to assess binding to, and effect on activity of, esterases in living cells, were known to one of skill in the art at the time of filing. One of ordinary skill in the art, reading the specification as filed and using the teachings available for example in Deutsch et al., would be able to use the claimed screening methods to identify compounds which are capable of binding the COE-2 polypeptide (SEQ ID NO:2).

In addition, Applicants respectfully point out that although the screening methods of the instant invention do not require description of an example of a product of such a screen, compounds known to bind to carboxylesterases as inhibitors (e.g., nordihydroguaiaretic acid (NDGA), tri-orthocresylphosphate (TOCP), bis-p-nitrophenylphosphate (BNPP) and tetrachlorvinphos (TCVP), please see pages 263-264 of Satoh et al., cited by the Examiner) and to esterases as substrates (e.g., fluorescein diacetate (FDA) and chloromethyl fluorescein diacetate (CMFDA), please see Deutsch et al., abstract) were well-known to one of ordinary skill in the art at the time of filing of the instant specification.

Thus, Applicants submit that the teachings of the specification as filed, in combination with the information known to those of skill in the art as described above, give the skilled artisan guidance and a reasonable expectation for success in combining a compound with a cell expressing the COE-2 polypeptide, as well as well-known methods for assessing not only binding to, but also modulation of the COE-2 esterase. Furthermore, Applicants submit that to use the claimed screening methods does not require any undue experimentation.

Applicants therefore submit that the specification does in fact teach how to use the method of the present invention, with specific examples and guidance as outlined above along with the teachings and guidance available to the skilled artisan at or before the time of filing, thus the specification is fully enabling to one of ordinary skill in the relevant art to use the claimed invention — the screening methods using the COE-2 polypeptide. Applicants respectfully request reconsideration and withdrawal of the rejection of claims 38-40, 43, and 46-48 under 35 USC §112, first paragraph.

CONCLUSIONS

In view of the remarks made herein, Applicants respectfully submit that the rejection presented by the Examiner is now overcome and that this application is in condition for allowance. If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned.

This paper is being filed timely as a request for a three month extension of time is filed concurrently herewith. No additional extensions of time are required. In the event any additional extensions of time are necessary, the undersigned hereby authorizes the requisite fees to be charged to Deposit Account No. 501668.

Entry of the remarks made herein is respectfully requested.

Respectfully submitted,

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MILLENNIUM PHARMACEUTICALS, INC.

By /Mario Cloutier/

Mario Cloutier
Registration No. 57, 225
40 Landsdowne Street
Cambridge, MA 02139
Telephone - 617-577-3522
Facsimile - 617-551-8820